PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference P17733 DrB/b	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2004/010700	International filing date *(day/month/year)* 23 September 2004 (23.09.2004)	Priority date *(day/month/year)* 23 September 2003 (23.09.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant TECHNISCHE UNIVERSITAET MUENCHEN		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 27 March 2006 (27.03.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Ellen Moyse Telephone No. +41 22 338 89 75

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/010700	23.09.2004	23.09.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/28, A61K39/395, C12N15/13, C12N5/18, G01N33/50, A61P31/04

Applicant
TECHNISCHE UNIVERSITAET MUENCHEN

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for International preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Montrone, M Telephone No. +49 89 2399-8711

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/010700

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 23-30(all partially)

because:

☒ the said international application, or the said claims Nos. 23-30(all partially) with respect to IA relate to , the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,6,7,30
	No:	Claims	1,2,4,5,8-29,31
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-31
Industrial applicability (IA)	Yes:	Claims	1-22,31
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claims 23 to 30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Re Item V.

Reference is made to the following documents:

D1: WO 01/36488 A
D2: WO 03/070761 A
D3: BRIGHTBILL HANS D ET AL: SCIENCE, vol. 285, no. 5428, 30 July 1999 , pages 732-736
D4: ALIPRANTIS A O ET AL: SCIENCE, vol. 285, no. 5428, 30 July 1999, pages 736-739
D5: UEHORI JUNJI ET AL: INFECTION AND IMMUNITY, vol. 71, no. 8, August 2003, pages 4238-4249
D6: SANDOR FRANTISEK ET AL: JOURNAL OF CELL BIOLOGY, vol. 162, no. 6, 15 September 2003, pages 1099-1110
D7: MATSUGUCHI TETSUYA ET AL: BLOOD, vol. 95, no. 4, 15 February 2000 , pages 1378-1385
D8: MENG GUANGXUN ET AL: THE JOURNAL OF CLINICAL INVESTIGATION, vol. 113, no. 10, May 2004, pages 1473-1481

1. Novelty (Art. 33(2) PCT)

Claim 1 refers to a cross-reactive antibody specifically inhibiting the mammalian Toll-like receptor 2 (TLR2)-mediated immune response by binding to the C-terminal portion of the extracellular domains of at least human and murine TLR2.

D1 refers to antagonistic anti-TLR2 antibodies being cross reactive with human and murine TLR2. Moreover, D1 mentions the advantage of having said cross reactive

antibodies (see page 7, line 4 to page 8, line 9). They can be raised against the extracellular domain of TLR2 (see page 9, lines 4 to 7). They can be therapeutically used for the treatment of microbial infections, like septic shock either alone or in combination with other anti-bacterial agents (see page 13, line 4 to page 16, line 35, page 19, lines 3 to 13, example 2). In consequence, D1 is considered to be detrimental to the novelty of the subject-matter of claims 1, 2, 4, 5, 8 to 29.

D2 discloses further antagonistic anti-TLR2 antibodies (see page 9, lines 1 to 3, page 21, lines 17 to 19 and example 4). Thus, D2 is considered to be detrimental to the novelty of the subject-matter of claims 1, 2, 4, 5.

D3 discloses an assay for the detection of antagonistic anti-TLR2 antibodies (see abstract, fig. 2, page 734, col. 2, first para.). Thus, D3 is considered to be detrimental to the novelty of the subject-matter of claim 31.

D4 discloses an assay for the detection of antagonistic anti-TLR2 antibodies (see abstract, fig. 1, page 737, col. 1, first para.). Thus, D4 is considered to be detrimental to the novelty of the subject-matter of claim 31.

D5 discloses further antagonistic anti-TLR2 antibodies either alone or in combination with an anti-TLR4 blocking antibody and assays for the testing of blocking activities (see abstract, page 4239, col. 2, first para. to fourth para., table 2, page 4242, col. 2, second and third para., page 4245, col. 1, second para. to col. 2, second para., page 4248, col. 2, first para.). In consequence, D5 is considered to be detrimental to the novelty of the subject-matter of claims 1, 2, 4, 5, 18 to 23 and 31.

D6 discloses a further antagonistic anti-TLR2 antibody and an inhibition assay (see page 9, lines 1 to 3, page 21, lines 17 to 19 and example 4). Thus, D2 is considered to be detrimental to the novelty of the subject-matter of claims 1, 2, 4, 5 and 31.

In summary, the subject-matter of claims 1, 2, 4, 5, 8 to 29 and 31 is not considered to be novel and does not comply with the requirements of Art. 33(2) PCT.

2. Moreover, the subject-matter of claims 1 to 31 appears not to be inventive for the

following reasons:

D1 is the considered to be the closest prior art. It refers already to cross reactive antibodies blocking specifically TLR2. The subject-matter of claim 3 is distinguished therefrom in that it refers to sequences coding for the variable heavy and/or light chains of a further cross reactive anti-TLR2 antibody.
The objective problem to be solved was thus the isolation of further cross protective antagonistic anti-TLR2 antibodies.
However, the skilled person had a strong motivation to isolate this antibodies for their broad applicability as a research tool in mice and their therapeutic effect in treating human patients. Moreover, the sequences of human and mice TLR2 were known from the prior art. D7 clearly mentions the high degree of similarity between the extracellular domain of mouse and human TLR2 (see page 1380, col. 1, fourth para. and fig. 1, page 1383, col. 1, second para.). Consequently, the skilled person had only to select the sequence parts being identical between humans and mice and after immunogenisation of mice to isolate the antibodies showing the desired properties. This, is considered to be a mere standard technique in the art which cannot be used for rendering the claimed sequences inventive over the existing prior art (Art. 33(3) PCT). The same arguments apply to the subject-matter of claims 6 and 7. In addition, The subject-matter of claim 30 does not appear to add anything to the subject-matter of claim 1 which would render this claim inventive in the light of the cited documents. Thus, said claim does not fulfil the requirements of Article 33(3) PCT either.

3. For the assessment of the present claims 23 to 30 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. The applicant is reminded that he may respond to this opinion only if he intends to enter the Chapter II PCT phase.